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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/816,785	03/22/2001	Ira J. Fox	UNMC -0032	5547

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EXAMINER

LI, QIAN JANICE

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 02/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/816,785	FOX ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 20 December 2004.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-26 is/are pending in the application.
- 4a) Of the above claim(s) 1-7,9-13,15,23,24 and 26 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 8, 14, 16-22, 25 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                        | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)               | Paper No(s)/Mail Date. _____  |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>8/1/01</u> .  | 6) <input type="checkbox"/> Other: _____                                    |

### **DETAILED ACTION**

Applicant's election of Group II and species election drawn to a population of functional human hepatocytes or immortalized human hepatocytes, without traverse in the response filed 12/20/04 is acknowledged. It is noted there is a typographic error in the Restriction Requirement mailed 10/21/04, i.e. claim 14 (drawn to a population of functional hepatocytes), but not claim 15 (drawn to a method of treating a patient, belong to group III), should be included in group II. Accordingly, Claims 1-7, 9-13, 15, 23, 24, and 26 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse.

Claims 8, 14, 16-22, 25 are under current examination.

### ***Claim Rejections***

Claims 8 and 14 are objected to because they depend from a claim drawn to a non-elected invention. Upon election of an invention for examination in this application, the claims should be amended so that they only read on the elected invention.

Claim 25 is objected to, the phrase, "and is" or "wherein the reverse-immortalized hepatocyte is" should be inserted before "produced" in line 2.

### ***Claim Rejections - 35 USC § 102/103***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 8, 14, and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by or in the alternative under 35 U.S.C. 103(a) as obvious over *Yurasov et al* (Blood. 1997 Mar 1;89(5):1800-10).

These claims are drawn to a population of functional hepatocytes that underwent an immortalized and disimmortalized process, wherein the claim limitation for said population would be hepatocytes that are functioning. Given the broadest reasonable interpretation, these cells may or may not contain a DNA construct because a DNA construct introduced during the immortalization process usually is not stable in the cell, and will be eliminated fairly soon from the cell; wherein if the hepatocytes contain a DNA construct, such construct does not contain a removable DNA segment comprising an oncogene, preferably the hepatocytes are human hepatocytes.

*Yurasov et al* teach a population of functional human fetal liver cells (HFL) comprising hepatocytes (2<sup>nd</sup> paragraph, page 1801), wherein some of the HFL cells are transduced with a retrovirus-derived DNA vector that does not contain a removable

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DNA segment. Both populations (transduced or non-transduced HFL) contain hepatocytes that are structurally and functionally indistinguishable from the claimed population. Accordingly, *Yurasov et al* anticipate instant claims.

It is noted that the prior art liver cell population differs from the claimed population only by the method of manufacture. However, the claimed method of making the functional liver cells would not distinguish them over the transduced human fetal liver cells taught by the prior art because they are phenotypically indistinguishable. See *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985), which teaches that a product-by-process claim may be properly rejectable over prior art teaching the same product produced by a different process, if the process of making the product fails to distinguish the two products. Thus, the claimed invention as a whole was at least *prima facie* obvious, if not anticipated, by the references, in the absence of sufficient, clear and convincing evidence to the contrary.

Applicants are reminded that the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the prior art products do not necessarily or inherently possess characteristics of claimed product, which requires factual evidence demonstrating that actual, unobvious differences exist or the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re

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Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

Claims 8, 14, and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by or in the alternative under 35 U.S.C. 103(a) as obvious over *Adams et al* (Proc Natl Acad Sci U S A. 1992 Oct 1;89(19):8981-5).

*Adams et al* teach a population of isolated human primary hepatocytes (column 2, page 8981), which then transduced with two retrovirus-derived DNA vectors that do not contain a removable DNA segment containing an oncogene (page 8982). These hepatocytes are structurally and functionally indistinguishable from the claimed population. Accordingly, *Adams et al* anticipate instant claims.

Again, the prior art hepatocyte population differs from the claimed population only by the method of manufacture. However, the claimed method of making the functional liver cells would not distinguish them over the transduced human hepatocytes taught by the prior art because they are phenotypically indistinguishable. See *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985), which teaches that a product-by-process claim may be properly rejectable over prior art teaching the same product produced by a different process, if the process of making the product fails to distinguish the two products. Thus, the claimed invention as a whole was at least *prima facie* obvious over, if not anticipated, by the references in the absence of sufficient, clear and convincing evidence to the contrary.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

- (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 16-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Anderson* (USP 5,629,159, IDS), in view of *Nakamura et al* (Transplant 1996;63:1541-7, IDS), and *Adams et al* (Proc Natl Acad Sci U S A. 1992 Oct 1;89(19):8981-5) or *Yurasov et al* (Blood. 1997;89(5):1800-10).

*Anderson* teaches the need in the art for immortalizing and then disimmortalizing mammalian cells. *Anderson* teaches that the exogenous nucleic acid used in gene therapy is often carried by the cells of a patient's own, and for the purpose of expansion and genetic manipulation, these cells are often immortalized, which may be oncogenic when transplanted back to the patient (Introduction). Accordingly the invention provided methods and cells that may be disimmortalized. *Anderson* discloses a population of immortalized primary murine fibroblast cells transformed with a DNA construct integrated into the genome of said cell, wherein the construct comprises two

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recombinase target sites (loxP) flanking an oncogene v-myc, (e.g. claim 1, and column 15, lines 11-17), which confers immortalization to said cell; wherein the construct further comprises a selectable marker (e.g. claim 2), and a suicide gene (HPV-tk, column 5, lines 25-38). *Anderson* teaches the immortalization is reversible by introducing a Cre recombinase expression construct into said cell (column 15, lines 61-63, and claims 10-18) and remaining cells containing the oncogene can be destroyed by exposure to gancyclovir. *Anderson* goes on to teach that suitable cells for practicing the claimed invention include any cell type that does not produce a recombinase recognizing the target sequence in the construct, wherein the cells may be obtained from vertebrate, mammalian, and preferably human cells (column 12, lines 32-44). The disclosure of *Anderson* differs from the claimed invention in that he does not particularly name or transduce hepatocytes.

*Nakamura et al* supplemented the teachings of *Anderson* by establishing the desirability and feasibility in the art to use conditional immortalized hepatocytes for treating liver disease. *Nakamura et al* implanted transduced rat hepatocytes with a replication-defective retroviral vector encoding a thermolabile mutant SV40 T antigen, which confers a reversible immortalization. *Nakamura et al* go on to teach that the transduced hepatocytes significantly improve the survival of rats with acute liver failure (e.g. abstract and fig. 1). *Nakamura et al* teach that this strategy provides an alternative for the shortage of liver donor in humans (1<sup>st</sup> paragraph, page 1541, column 2).



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*Adams et al* or *Yurasov et al* supplemented the teachings of *Anderson* by illustrating the feasibility of transducing human primary hepatocytes with a DNA construct.

Claim 22 recites a particular immortalized human liver cell line, NKNT-3, which is produced by transducing human primary hepatocytes with the construct as taught by *Anderson*. Although the combined teachings of *Anderson* in view of *Nakamura et al* and *Yurasov et al* do not disclose a particular cell line named as NKNT-3, the skilled artisan following the combined teaching would have a reasonable expectation of success to produce a human liver cell line that is a functional equivalent of NKNT-3. Given the knowledge of the skilled in the art, this limitation would fall within the bounds of the optimization.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the methods as taught by *Anderson*, in expanding and genetically manipulating human hepatocytes as taught by *Adams et al* and *Yurasov et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the advantage of the immortalization-disimmortalization system as taught by *Anderson*. Given the success as taught by *Nakamura et al*, *Adams et al*, and *Yurasov et al*, the skilled artisan would have had a reasonable expectation of success in transducing primary human hepatocytes with the construct as taught by *Anderson*. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

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### ***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Ram R. Shukla** can be reached on 571-272-0735. The fax numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

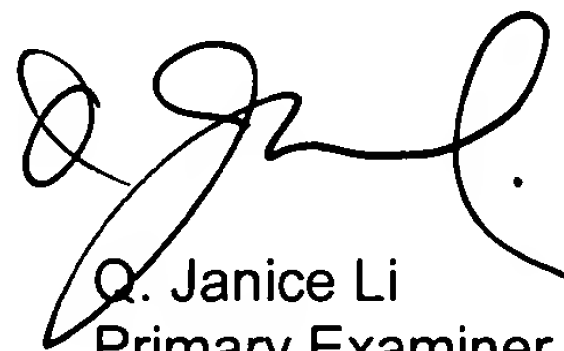
Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Q. Janice Li  
Primary Examiner  
Art Unit 1632



February 3, 2005